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Original Research

Induction of Labor According to Medical Indications: A Critical Evaluation through a Prospective Study

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Abstract

Background: The induction of labor (IOL) is a common obstetric intervention, steadily increasing (one out four pregnancies) in the last years. This procedure should be considered only when there is a medical indication, and when the benefits outweigh the maternal and/or fetal risks of waiting for spontaneous onset of labor. Therefore, this study aims to compare the efficacy of the IOL in terms of induction to delivery time, mode of delivery, and neonatal well-being among different evidence-based and non-evidence-based indications. **Methods**: This prospective study was conducted at the University Hospital of Modena, between January and December 2020. We included singleton pregnant women undergoing IOL, at the term. Intrauterine deaths, small for gestational age fetuses <5th centile as well women with hypertensive disorders were excluded. Women have been subdivided into 3 groups based on the indication to IOL: premature rupture of membranes (PROM), post-date pregnancy (>41 weeks + 3 days), and *non-evidence-based* indications (NEBI). The primary outcome is the time occurring between IOL and delivery (TIME), analyzing separately by parity. Moreover, mode of delivery and neonatal well-being were evaluated. **Results**: A total of 585 women underwent IOL in the study period. Overall, the median TIME between IOL and delivery was 19 hours, and the mean cesarean section CS rate was 15.5% (91/585). Pregnancies induced for postdate and non-evidence-based indications registered respectively a significantly higher mean time ($p < 0.001$), compared with women induced for PROM. This occurred both in nulliparous and multiparous women. Moreover, at multivariate analysis, the IOL TIME ≥24 hours was significantly influenced by Bishop score ($p = 0.000$) and NEBI ($p = 0.02$) in nulliparous and by gestational age ($p = 0.000$) and NEBI ($p = 0.02$) in multiparous. Moreover, CS rate was significantly influenced by Bishop score ($p = 0.003$) in nulliparous and by gestational age ($p = 0.01$) in multiparous. Finally, neonatal intensive care unit (NICU) admission resulted significantly influenced only by gestational age ($p = 0.002$) in multiparous. **Conclusions**: Our study confirms that IOL in non-evidence-based indications, leads to an increase in induction to delivery time comparing with women induced for PROM, both in nulliparous and multiparous women, thus it should be justified and carefully evaluated. Further randomized controlled trials (RCT) conducted in European/Italian settings are needed to determine the perinatal outcomes of IOL in non-evidence-based indications.

Keywords: induction of labor; non-evidence-based indication; PROM; post-term pregnancy; ARRIVE trial; parity; cesarean section; the time between induction and delivery; NICU admission

1. Introduction

The induction of labor (IOL) is a common obstetric intervention, steadily increasing (counting approximately one out four pregnancies) in the last years. The Italian rate is overall 24.8% of the 347.772 deliveries (82.077 women) [1] in 2018 and, even in the Emilia-Romagna region, induction represents 29.6% of deliveries in 2020 [2].

According to WHO [3], this procedure should be considered only when there is a medical indication, and when the benefits outweigh the potential maternal and/or fetal risks of waiting for spontaneous onset of labor. Although indications to the IOL progressively increased, most of them lack supporting evidence. Indeed, Italian scientific societies [4] recommend IOL with a good quality of evidence in case of postdate pregnancy, premature rupture of membranes (PROM) at term, hypertensive disorders, and pre-pregnancy diabetes mellitus. Other indications such as gestational diabetes, small for gestational age, cholestasis in pregnancy, oligo/polyhydramnios, suspected macrosomia, assisted reproductive technology (ART), and twins pregnancy reach only low or moderate quality of evidence, thus are not considered as strong indication [5].

Moreover, after the recent publication in the Journal of New England of Medicine of the ARRIVE trial [6], also women with no medical indication for delivery were considered for induction at 39 weeks, because the results of this large American randomized controlled trial, demonstrated better outcomes in IOL group (lower CS rate of 16%, lower

hypertensive disorders of 46% and similar neonatal complications) respect than the expectant management (EM) group. However, this trial presents some controversial aspects that may undermine the external validity of this policy at the wide population level [7], because of the different demographic parameters, sociocultural environment, perinatal mortality, and obstetric risk factors of the study population respect the general population, namely the European one.

Indeed, in the ARRIVE trial, the socioeconomic status and maternal age were significantly lower, while body mass index was significantly higher, and the hypertensive disorders were more frequent concerning the Italian cohort. as demonstrated by Tassis *et al.* [8] and Facchinetti *et al.* [9].

Finally, against the universal induction policy, a general perception of "limited satisfaction" of the antenatal care has been reported among women with induced labor [10,11], first, because most women planned physiological labor and birth while acknowledging that birth can be "unpredictable and frightening" [12,13] (and these beliefs give a reason as to why 73% of the >22,000 eligible women refused randomization in the ARRIVE Trial); second because this practice in patients with an unfavorable cervix requires cervical ripening, which takes time, leading to the longer length of stay before delivery. Moreover, the time from induction to delivery depends on parity as well as on different methods used, including mechanical methods (cervical balloon, amniotomy), pharmacological (prostaglandins, oxytocin) [5], and non-conventional practice such as acupuncture namely in postdate pregnancy [14].

Therefore, this study aims to compare the efficacy of the IOL in terms of induction to delivery time, mode of delivery (vaginal or cesarean section), and neonatal well-being among different evidence-based and non-evidence-based indications.

2. Material and Methods

This prospective study was conducted at the University Hospital of Modena, between January and December 2020. We included singleton pregnant women undergoing IOL, at the term of gestation (≥37 weeks). Intrauterine deaths, SGA fetuses <5th centile as well women with hypertensive disorders were excluded (Fig. 1).

Women have been subdivided into 3 groups based on the indication to IOL: premature rupture of membranes (PROM) that exceeds 24 hours (or <6 hours in women positive for group B streptococcus), post-date pregnancy (>41 weeks + 3 days), and non-evidence-based indications (NEBI). The NEBI included the indications for induction that, as showed by a recent systematic review (Coates D), need further adequately powered trials to demonstrate the benefit of terminating pregnancy compared with expectant management. These are the following: gestational diabetes mellitus under metabolic control with diet (GDM),

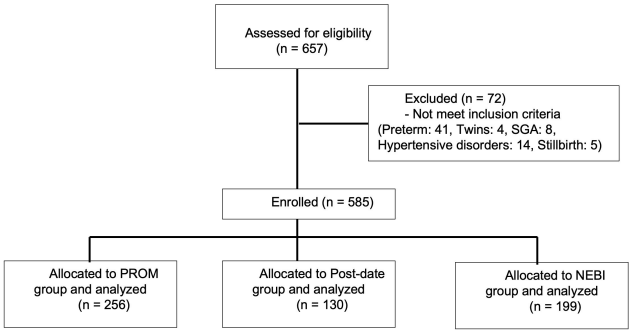

Fig. 1. Flow chart.

mild cholestasis of pregnancy (with bile acids <40 mmol/L) [15], obesity [16], medically assisted procreation, isolated polyhydramnios/oligohydramnios, and suspected macrosomia [5].

The diagnosis of PROM was confirmed by visualization of amniotic fluid passing from the cervical canal and pooling in the vagina, a basic pH test of vaginal fluid, or arborization (ferning) of dried vaginal fluid, which is identified under microscopic evaluation. Rupture of membranes was considered as a delivery indication when spontaneous labor occurred more than 24 hours after PROM. The post-date pregnancy was defined as 41 weeks + 3 weeks of gestation. Gestational age was based either on the first-trimester ultrasound scan or, in women with a regular cycle, on the first day of the last menstrual period if the expected date of delivery differed less than 7 days from that estimated by ultrasound.

Protocol for induction of labor was summarized in supplementary material.

The primary outcome is the time occurring between IOL and delivery (TIME), analyzing separately nulliparous and multiparous women. Moreover, mode of delivery and neonatal well-being through the Apgar at the 5th minute less than 7 and admission to neonatal intermediate or intensive care unit (NICU) were evaluated. As indicated by previous studies, these outcomes are associated with significant risks of neonatal mortality or long-standing adverse health complications, including hypoxic-ischemic encephalopathy [17].

The authors have complied with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research involving human subjects. Approval from the local Institution Review Board was obtained (n: 25094 of 16/9/2020).

As we stratified neonatal outcomes according to delivery indications, we also compared how maternal, fetal, and neonatal characteristics varied in the case of PROM, post-date, or NEBI. Categorical variables were presented as n (%) and tested with the Chi-square test or Fisher's exact test as appropriate. Normally distributed continuous variables were presented as mean ± SD and compared with One Way ANOVA and posthoc Bonferroni test. Non-normally dis-

Table 1. Population characteristics.

	PROM (n = 256)	Post-date pregnancy (n = 130)	Non-evidence based indication (n = 199)	*p* value
Nulliparous (N = 351)				
Mean maternal age	32.3 ± 5.3	33.5 ± 5.3	34.4 ± 6.8	0.02
Country of origin				
Italy	104 (62.6)	50 (60.2)	64 (61.5)	0.39
Other	62 (37.4)	33 (39.8)	40 (38.5)	
Pre-pregnancy BMI	24.4 ± 4.7	23.9 ± 3.9	25.5 ± 6.4	0.09
Obesity (BMI ≥30)	16 (9.6)	8 (9.6)	17 (17.3)	0.31
BMI at delivery	28.6 ± 5.0	28.0 ± 5.1	29.7 ± 6.7	0.08
Mean gestational age	39.1 ± 1.1	41.0 ± 0.3	39.4 ± 1.2	**<0.001**
Mean bishop score	3.9 ± 1.7	2.6 ± 1.7	3.1 ± 2.2	**0.0002**
Mild cholestasis	2 (1.2)	2 (1.5)	3 (1.5)	0.73
GDM	14 (8.5)	6 (7.2)	11 (10.6)	0.27
ART	2 (1.2)	1 (1.2)	2 (1.9)	0.56
Suspected Macrosomia	12 (7.2)	6 (7.2)	11 (10.5)	0.19
Isolated poly/oligohydramnios	1 (0.6)	0	2 (1.9)	0.15
Multiparous (N = 235)				
Mean maternal age	32.2 ± 4.8	33.4 ± 4.6	33.9 ± 5.2	0.07
Country of origin				
Italy	39 (43.5)	18 (39.5)	41 (41.8)	0.31
Other	51 (56.5)	28 (60.5)	57 (58.1)	
Pre-pregnancy BMI	25.3 ± 4.9	24.2 ± 4.7	28.6 ± 6.7	**<0.001**
Obesity (BMI ≥30)	17 (18.9)	6 (13.0)	41 (41.8)	**<0.001**
BMI at delivery	28.9 ± 4.7	27.9 ± 4.4	31.4 ± 6.7	**0.001**
Mean gestational age	39.0 ± 1.0	40.9 ± 0.1	38.9 ± 1.4	**<0.001**
Mean bishop score	4.0 ± 1.7	3.8 ± 1.9	3.4 ± 1.7	0.23
Mild cholestasis	2 (1.2)	1 (0.8)	3 (1.5)	0.58
GDM	8 (8.8)	4 (8.7)	10 (10.2)	0.38
ART	0	0	1 (1.0)	0.45
Suspected Macrosomia	7 (7.7)	4 (8.6)	8 (10.2)	0.21
Isolated poly/oligohydramnios	0	1 (2.2)	1 (1.0)	0.29

Continuous variables are reported as mean ± SD.

Categorical variables are reported as numbers (%).

Bold numbers reach statistical significance ($p \leq 0.05$).

tributed variables were reported as median and inter quartile range (IQR) and compared with Kruskal-Wallis test. A level of statistical significance of $p \leq 0.05$ was considered. A final multivariate analysis was carried out to evaluate the main clinically and statistically relevant variables contributing to the "Induction to delivery time ≥24 h", the "Cesarean section", the "NICU admission". Results of logistic models were reported as the Odds Ratio (OR) with 95% confidence interval and Wald *p*-value.

3. Results

A total of 585 women underwent IOL in the study period. Table 1 summarizes maternal characteristics subdivided by parity. Among the 351 cases of nulliparous women the three study groups significantly differ in mean maternal age ($p = 0.02$), mean gestational age at delivery ($p < 0.001$), and mean bishop score ($p = 0.0002$). While in the 235 remnants multiparous cases significant differences were found in pre-pregnancy body mass index (BMI) ($p < 0.001$), obese women ($p < 0.001$), BMI at delivery ($p = 0.001$), and mean gestational age at delivery ($p = 0.000$).

No significant differences were found in the frequency of obstetrics NEBI conditions (mild cholestasis, gestational diabetes mellitus (GDM), assisted reproductive technologies (ART), suspected macrosomia and isolated poly/oligohydramnios) in the three groups, except for obesity.

Overall, the median TIME between IOL and delivery was 19 hours, and the mean CS rate was 15.5% (91/585).

In the univariate analysis, shown in Table 2 (Ref. [6]), the main perinatal outcomes were presented according to delivery indication and parity. Overall, pregnancies induced for *postdate* and non-evidence-based indications registered respectively a significantly higher median time: 19 (10–36) hours and 17 (10–35); $p < 0.001$, compared with

Table 2. Perinatal outcomes in study groups according to parity.

	PROM (n = 256)	Post-date pregnancy (n = 130)	Non-evidence based indication (n = 199)	*p* value
Induction to delivery time* (h)	10 (6–18)	19 (10–36)	17 (10–35)	<0.0001
CS rate**	30/256 (11.7%)	25/130 (19.2%)	36/199 (18.1%)	0.19
Apgar < 75th minute**	4/256 (1.6%)	3/130 (2.3%)	8/199 (4%)	0.26
Adimission to neonatal intensive care unit**	0/256 (0%)	3/130 (2.3%)	6/199 (3%)	0.02
Intermediate neonatal unit**	4/256 (1.6%)	0/130 (0%)	2/199 (1%)	0.35
Nulliparous (N = 351)				
Induction to delivery time* (h)	12 (8–21)	27 (15–41)	26.5 (15–41)	<0.0001
CS rate**	23/166 (13.9%)	21/83 (25.9%)	25/104 (24%)	0.05
Apgar < 75th minute**	4/166 (2.4%)	2/83 (2.4%)	4/104 (3.8%)	0.76
Adimission to neonatal intensive care**	0/166 (0%)	2/83 (2.4%)	4/104 (3.8%)	0.05
Intermediate neonatal unit**	4/166 (2.4%)	0/83 (0%)	0/104 (0%)	0.24
Multiparous (N = 235)				
Induction to delivery time* (h)	7 (4–11)	11 (6–15)	14.5 (8–27)	0.001
CS rate**	7/90 (7.7%)	4/47 (8.5%)	11/95 (11.5%)	0.78
Apgar < 75th minute**	0/90 (0%)	1/47 (2.1%)	4/95 (4.2%)	0.15
Adimission to neonatal intensive care**	0/90 (0%)	1/47 (2.1%)	2/95 (2.1%)	0.38
Intermediate neonatal unit**	0/90 (0%)	0/47 (0%)	2/95 (2.1%)	0.58

* Values are given as median and IQR. ** Values are given as numbers (%).

Induction to delivery time (h) has been calculated only for women with vaginal delivery, excluding CS and Operative deliveries.

Intermediate neonatal unit: area organized and equipped to provide constant care and treatment for mild to moderately ill infants not requiring neonatal intensive care such as jaundice, late preterm, hypoglycemia requiring endovenous infusion, transient tachypnea, abstinence neonatal syndrome, congenital minor cardiopathies, need to improve feeding competences, newborns of HIV positive mothers [6].

women induced for PROM, 10 (6–18) hours, evaluated only among vaginal spontaneous deliveries (450 cases). This occurred both in nulliparous and multiparous women. Moreover, overall, pregnancies induced for postdate and non-evidence-based indications registered respectively a significantly higher rate of admission to NICU (2.3% and 3%; $p = 0.02$) compared with women induced for PROM (0%). This occurred only in nulliparous women ($p = 0.05$).

Furthermore, in nulliparous, the CS rate in the PROM group was significantly lower than in the postdate group and the NEBI group ($p = 0.05$). Similarly, admission to NICU resulted significantly lower in PROM group respect than in the postdate and the NEBI group (0 cases), respect then in postdate group (2 cases of Agar score 5' <3 and 1 case of suspected sepsis) and in NEBI group (3 cases of needing of respiratory support, 2 case of Apgar score 5' <3 and 1 case of suspected sepsis) ($p = 0.05$). Apgar <7 at 5' score and the intermediate neonatal need did not differ between groups.

Table 3 reported the multivariate logistic regression models that investigated the role of maternal age, gestational age at delivery, pre-pregnancy BMI, BMI at delivery, Bishop score, and IOL indication, on the IOL TIME, CS, and NICU admission in nulliparous and multiparous women. The IOL TIME ≥24 hours was significantly influenced by bishop score ($p = 0.000$) and NEBI ($p = 0.02$) in nulliparous and by gestational age ($p = 0.000$) and NEBI ($p = 0.02$) in multiparous. Moreover, CS rate was significantly influenced by Bishop score ($p = 0.003$) in nulliparous and by gestational age ($p = 0.01$) in multiparous. Finally, NICU admission resulted significantly influenced only by gestational age ($p = 0.002$) in multiparous.

4. Discussion

Our study highlights that the IOL performed for non-evidence-based indications (NEBI) represent about 30% of the inductions in this study population and this datum is comparable to that reported in the literature [18].

The rate of NEBI IOL is progressively increasing, with a crescent need of resources in the Hospital such as additional rooms [19]. Thus, to counteract this phenomenon, it was proposed for the induction of nulliparous, the outpatient cervical ripening, however, only two small sample size trials on its safety have been performed [20,21].

Moreover, our data confirm the literature highlighting that NEBI IOL compared with IOL for PROM, have longer induction to delivery time (TIME) both in nulliparous and multiparous women. Moreover, this TIME is influenced by the Bishop score and gestational age, in line with other study results such as Rossi RM *et al*. [22] who provided a risk calculator for CS, available online (https://ob.tools/iol-calc) for health care providers in counseling

Table 3. Multivariate analysis of the effect of gestational age and circumstances at delivery on neonatal outcomes.

	Induction to delivery time ≥24 h		Cesarean section		NICU admission	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
			Nulliparous			
Maternal age (+1 year)	1.05 (0.9–1.1)	0.33	1.0 (0.9–1.2)	0.30	0.9 (0.7–1.2)	0.53
Gestational age (+1 week)	0.99 (0.8–1.1)	0.86	0.9 (0.8–1.1)	0.41	0.9 (0.7–1.2)	0.97
Bishop score (+1 point)	0.37 (0.2–0.6)	0.000	0.5 (0.4–0.8)	0.003	0.7 (0.3–1.8)	0.49
NEBI	2.4 (1.1–5.1)	0.02	1.5 (0.7–3.2)	0.32	1.6 (0.2–8.9)	0.65
POST-TERM	1.4 (0.8–1.6)	0.47	1.1 (0.7–1.8)	0.50	0.6 (0.2–2.3)	0.46
PROM	§		§		§	
			Multiparous			
Pre-pregnancy BMI (+1)	1.1 (0.9–1.2)	0.22	1.1 (0.9–1.2)	0.32	0.96 (0.7–1.3)	0.86
BMI at delivery (+1)	1.0 (0.9–1.1)	0.52	0.9 (0.9–1.0)	0.64	1.0 (0.9–1.1)	0.33
Obesity (BMI ≥30)	1.4 (0.8–2.3)	0.17	1.1 (0.9–1.1)	0.59	1.3 (0.8–2.1)	0.21
Gestational age (+1 week)	0.8 (0.8–0.9)	0.000	0.9 (0.8–0.9)	0.01	0.8 (0.7–0.9)	0.002
NEBI	1.8 (1.2–2.8)	0.008	1.6 (0.9–2.8)	0.23	1.5 (0.3–6.7)	0.62
POST-TERM	1.2 (0.7–1.5)	0.52	1.3 (0.9–1.5)	0.33	0.8 (0.5–1.3)	0.45
PROM	§		§		§	

Multivariate logistic regression models investigating the role of maternal age, gestational age at delivery, pre-pregnancy BMI, BMI at delivery, Bishop score, and non-evidence-based indication, on the Induction to delivery time, cesarean section, and NICU admission in nulliparous and multiparous women.

§: reference group.

women who are undergoing induction of labor. Indeed, this score includes the Bishop score and gestational age in addition to other 5 factors.

Moreover, it is worth pointing out that PROM patients of our study seem to have a more favorable prognosis, probably related to the membrane rupture itself, which is usually a strategy used to accelerate labor in women with intact membranes.

Our data are in line with ARRIVE trial [6] where the induced women without indications present a reduced cesarean section rate of 16% and similar neonatal complications respect the expectant management group. Indeed, in our population, CS rate and NICU admission were not increased in the NEBI IOL group and in Post date group comparing with PROM group.

It must be underlined that our population presents different maternal characteristics respect with to those of the IOL group of the ARRIVE trial. Women included in our NEBI group, were certainly older (mean age 33 vs. mean age at randomization 24 years), while less obese (mean BMI 25.1 vs. mean BMI at randomization of 30.5) than the IOL group population of the ARRIVE [9]. Therefore, this compensation could explain the similar results in terms of CS and neonatal outcomes in induced patients with respect than other controls group, despite the different population characteristics (in ARRIVE trial, patients are younger but much more obese).

Those women, induced for NEBI, who delivered vaginally in our study, experimented with a significantly longer TIME respect than women induced for PROM, as already showed by Delorme P *et al*. and Papalia N *et al*. [23,24].

Moreover, in our population nulliparous women presented the same age as the multiparous one. A possible explanation is that in the Italian population, the mean age at first pregnancy is higher respect than in other countries (31.5 years) [12]. On the other hand, multiparous were more frequently foreign women and usually they had the first pregnancy before the Italians. Thus, foreign multiparous result having the same age as Italian nulliparous.

Aside from the impact of an aging population on the economics and burdens of society [25], age is positively associated with both increased CS rate [26] and occurrence of perinatal mortality such as stillbirths (SB) [26], however, in our study maternal age did not influence the perinatal outcome. Moreover, the obesity rate in our population is in line with European data (7.8%–25.5%) [27], and lower respect whit American data such as presented in the ARRIVE trial. This maternal characteristic, which was significantly represented in the multiparous population, at multivariate analysis did not influence the perinatal outcome. Thus, we hypothesize that, as speculated in the studies of Tassis *et al*. [8] and of Ghi *et al*. [7], the CS rate of the NEBI group was not worsened by BMI because these patients could benefit from the anticipate of delivery. Indeed, it is well-known that obesity represents one of the major risk factors for obstetric and perinatal complications [28]

including intrapartum stillbirth [29] and perinatal asphyxia [30].

The limitation of our study is the lack of detailed perinatal outcomes because more midwives participated in the study, and some data was neglected or poorly collected (pH, BE, etc.). The strengths are represented by the prospective design and the accuracy of collected data namely for the indications of the induction.

5. Conclusions

Our study confirms that IOL in non-evidence-based indications, leads to an increase in induction to delivery time comparing with women induced for PROM, both in nulliparous and multiparous women, thus it should be justified and carefully evaluated for counselling patients. Further randomized controlled trials (RCT) conducted in European/Italian settings are needed to determine the perinatal outcomes of IOL in non-evidence-based indications.

Author Contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission. Each author contributed significantly: FM, RP in data collection or management and manuscript writing; DM and GG in data analysis and manuscript writing and editing; FM, ES, GT in the project development and FF in project development and manuscript editing.

Ethics Approval and Consent to Participate

The authors have complied with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research involving human subjects. Approval from the local Institution Review Board was obtained (n: 25094 of 16/9/2020). Approval from the local Institution Review Board was obtained (n: 25094 of 16/9/2020) and written informed consent was obtained from each patient enrolled.

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Conflict of Interest

The authors declare no conflict of interest.

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